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A challenging case of ectopic ACTH-dependent Cushing's syndrome due to medullary thyroid carcinoma

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Medullary thyroid carcinoma (MTC) is an infrequent neoplasm originating from thyroid parafollicular cells. Calcitonin production is its distinguishing feature [1]. Due to its neuroendocrine provenience, MTC can release different active agents. Uncommonly, it can be a source of adrenocorticotropic hormone (ACTH), accounting for about 2% of ectopic Cushing's syndrome (CS) [1].

We present a case of a 45-year-old male with an ectopic ACTH-dependent CS induced by MTC. The patient, with a history of recent diabetes and hypertension, was referred to the Endocrinology Department for suspicion of CS. He complained of increasing weakness, aggravating facial plethora, and weight gain. A 4-mm pituitary microadenoma was confirmed by magnetic resonance imaging 2 years prior to admission.

A loss of cortisol circadian rhythm, abnormal results of 1-mg (serum cortisol 23.6 μg/dL) and 8-mg dexamethasone suppression test (cortisol 25.6 μg/dL), as well as moderately increased concentration of ACTH (103.0–122.0 pg/mL), were revealed. In the corticotropin-releasing hormone (CRH) stimulation test the ACTH concentration increased by more than 35%. Other laboratory tests results are presented in Table 1. The diagnosis of ACTH-dependent CS was confirmed, and metyrapone was implemented.

While searching for the source of ACTH secretion, positron emission tomography (PET/CT) with Gallium 68-tetraazacyclododecane-tetraacetic acid-octreotate ([^{68}Ga]Ga-DOTA-TATE) was performed, showing heterogeneous expression of somatostatin receptors in enlarged thyroid (Fig. 1). On neck ultrasound, a 20-mm hypoechogenic thyroid nodule with irregular margins and sparse central vascularization was noted. Due to the presence of pituitary microadenoma and the CRH stimulation test results, the patient was scheduled for bilateral inferior petrosal sinus sampling (BIPSS), during which no significant ACTH surge or lateralization was observed. Therefore, planned transsphenoidal surgery was cancelled. Shortly after, the patient was readmitted due to aggravation of CS. Markedly increased calcitonin (> 1000.0 pg/mL) and procalcitonin (23.70 ng/mL) concentrations were noted. Thyroid cytology was classified as Bethesda VI. After stabilization of his general condition, the patient underwent a total thyroidectomy. Histopathological examination confirmed MTC, and immunohistochemical staining for ACTH was positive in approximately 10% of cells (Fig. 2). Genetic screening for germline pathogenic variants of *RET* protooncogene was inconclusive. After thyroidectomy, hypercortisolaemia symptoms markedly subsided,

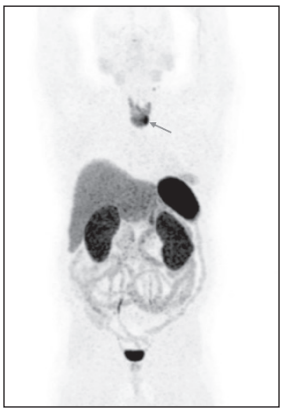

Figure 1. *[^{68}Ga]Ga-DOTA-TATEPET/CT showing heterogeneous expression of somatostatin receptors in the enlarged thyroid gland (arrow)*

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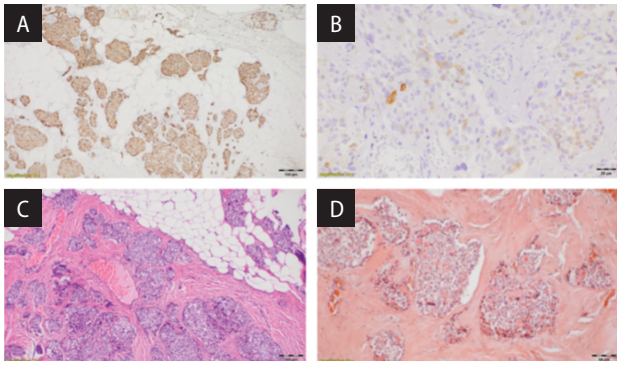

Figure 2. *Immunohistochemical staging of the medullary thyroid carcinoma (MTC). Tumour cells show positivity for calcitonin (***A***) (original magnification ×10) and adrenocorticotropic hormone (ACTH) (***B***) (original magnification ×40). Staining with haematoxylin and eosin (***C***) (original magnification ×10), and staining with Congo red (***D***) (original magnification ×20)*

and the patient developed transient secondary adrenal insufficiency. Mildly elevated calcitonin concentrations showed a downward trend. Post-operative whole-body CT scan was negative for local and distant metastases.

One and a half years after the surgery, Cushingoid features reappeared, and calcitonin, cortisol and ACTH concentrations markedly increased. Due to inoperative MTC local recurrence, vandetanib therapy has recently been initiated.

As the case illustrates, the first manifestation of MTC may be ectopic hypercortisolaemia. In the literature review by Barbosa et al., MTC-related CS accounted for 0.6% of all MTC patients [2].

Due to its rarity, diagnosing MTC-related CS can be difficult. Overlapping test results are the most common cause of Cushing's disease (CD) and ectopic ACTH-dependent CS (EAS) misdiagnosis, and unnecessary therapeutic procedures. ACTH-dependent CS prompts pituitary imaging. If a pituitary adenoma of < 6–9 mm is present, further diagnostic work-up is warranted. Tests that may distinguish between CD and EAS include the high-dose dexamethasone suppression test (HDDST) and CRH stimulation test. An overnight HDDST has a specificity of 100% to exclude EAS [3]. However, some patients with EAS achieve suppression in HDDST [4]. CRH stimulation test has a lower rate of misdiagnosis than overnight HDDST among patients with EAS (30% *vs*. 50%), but HDDST combined with CRH stimulation does not improve the diagnostic accuracy [4]. Increased plasma ACTH and cortisol concentrations after CRH stimulation usually indicate CD [4]. In cases with discordant results of pituitary imaging and CRH test, BIPSS is considered the gold diagnostic standard for distinguishing EAS from CD [4]. Another significant EAS imaging tool is PET/CT scan with [^{68}Ga]Ga-DOTATATE, which detects up to 65% of these tumours [5].

Table 1. *Other laboratory tests results*

Parameter	Values	Reference range
Glucose (mmol/L)	6.02	3.30–5.60
FSH (mIU/mL)	1.28	1.50–12.40
LH (mIU/mL)	0.30	1.70– 8.60
TSH (μIU/mL)	0.957	0.27–4.20
FT4 (pmol/L)	11.90	12.00–22.00
IGF-1 (ng/mL)	72.00	160.00–318.00
Testosterone (nmol/L)	3.30	8.64–29.00
ALT (U/L)	196.00	10.00–50.00
AST (U/L)	58.00	10.00–50.00
GGTP (U/L)	261.00	8.00–61.00

The reported case highlights the fact that despite the various diagnostic tools distinguishing between EAS and CS, it still poses a challenge. One should be aware of the inconsistent performance of diagnostic tests due to the variable biology of both ectopic ACTH-secreting tumours and pituitary adenomas. Cautious interpretation of laboratory tests and imaging results diminishes the likelihood of misdiagnosis. Furthermore, MTC should be considered as a potential cause of EAS, especially in patients with nodular goitre.

Author contributions

The authors' contributions to the work were as follows. Conception of the article — M.T-M., G.S.; design of the article, analysis of the data, writing of the manuscript — M.K.-C., P.S.; acquisition of data, analysis and interpretation of data — J.S., drafting the article or revising it critically for important intellectual content — M.T.-M., final approval of the version to be published — A.H.-D.

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Not applicable.

Conflict of interest

None declared.

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